

REMARKS

The Examiner rejected claims 1-4, 9, 12-21, and 24-35, and objected to claims 5-8 and 11. The Examiner also objected to the specification for lacking a Brief Description of the Drawings. Claims 3, 16-17, 27-28, and 30-35 are canceled herein without prejudice, and new claim 36 has been added. Thus, claims 1, 2, 4-9, 11-15, 18-21, 24-26, 29, and 36 are pending.

Claim 1 has been amended to recite a process for the preparation of multiple cross-linked HA that includes contacting HA with one or more chemical cross-linking agents so as to form two or more different types of functional bonds between HA molecules. Support for this amendment can be found in Applicant's specification at, for example, page 5, lines 3-10, which disclose that multiple cross-linked HA is a molecule of HA that is cross-linked to another molecule of HA by means of two or more different types of functional bond. Claim 1 also has been amended to incorporate the language of claim 3. In addition, claims 1, 7, 13, and 14 have been amended to correct punctuation and grammar, claims 1 and 24 have been amended with regard to the abbreviation for hyaluronic acid, and claim 24 has been amended with regard to its dependency. Claim 16 has been canceled and replaced with claim 36, which recites multiple cross-linked HA comprising an HA molecule cross-linked to a another HA molecule, wherein the HA molecules are crosslinked by at least two different types of bonds. Support for claim 36 can be found in previous claim 16 and throughout Applicant's specification. Further, a Brief Description of the Drawings has been added to page 4 of the specification. The drawings were included with the application as originally filed. The drawings also were described at page 25, lines 12-23 of the specification as originally filed. Thus, no new matter has been added.

In view of these amendments and the following remarks, Applicants respectfully request reconsideration and allowance of claims 1, 2, 4-9, 11-15, 18-21, 24-26, 29, and 36.

Objection to the Specification

The Examiner objected to the specification because the disclosure does not contain a Brief Description of the Drawings. Applicant has added a Brief Description of the Drawings to

page 4 of the application. Thus, Applicant respectfully requests that the Examiner withdraw the objection to the specification.

Rejection under 35 U.S.C. § 112, first paragraph

The Examiner rejected claims 27-28 and 33-34 under 35 U.S.C. § 112, first paragraph as failing to comply with the written description requirement. Specifically, the Examiner stated that the specification as originally filed does not support Applicant's claims to compositions in which an active agent is bound to cross-linked HA through physical or chemical means. The Examiner further stated that while the specification discloses that therapeutically active factors can be bound to cross-linked HA using methods well known in the art, no support is found for the narrower claim language that limits the binding to physical or chemical means.

Applicant respectfully disagrees. To further prosecution, however, claims 27-28 and 33-34 have been canceled herein without prejudice. Thus, the Examiner's rejection is moot.

Rejection under 35 U.S.C. § 102

The Examiner rejected claims 1-4, 12-13, 15-18, and 20-21 under 35 U.S.C. § 102(b) as being anticipated by the Tomihata *et al.* reference (*J. Biomed. Mater. Res.* 1997, 37:243-251). The Examiner stated that the Tomihata *et al.* reference discloses a cross-linked HA film containing amide and ester bonds. The Examiner also stated that the Tomihata *et al.* reference discloses that L-lysine methyl ester (cross-linking agent 1) was added to an 80 vol % ethanol / 20 vol % water mixture, and HA cross-linking was allowed to proceed in the presence of 10 mM water-soluble carbodiimide (cross-linking agent 2). Thus, the Examiner concluded that the present claims are not novel in view of the Tomihata *et al.* reference.

Applicant respectfully disagrees. To further prosecution, however, claim 1 has been amended to recite a process for the preparation of multiple cross-linked derivatives of HA, wherein the cross-linking is effected by contacting HA with one or more chemical cross-linking agents so as to form two or more different types of functional bonds between the HA molecules, and wherein the two or more different types of functional bonds are selected from the group consisting of ether, ester, sulfone, amine, imino, and amide bonds. Contrary to the teachings of

the Tomihata *et al.* reference, the procedures disclosed therein do not result in HA molecules cross-linked to one another by two or more types of bonds as set forth in present claim 1. In fact, a person having ordinary skill in the art would have known from U.S. Patent No. 6,096,727 (the '727 patent; copy enclosed) that cross-linking HA with carbodiimide does not result in ester bonds, but rather results in acylurea bonds. A person of ordinary skill also would have known that when HA is incubated with both carbodiimide and a nucleophile such as L-lysine methyl ester, the acylurea bonds are replaced with amide bonds. *See, e.g.*, column 3, lines 30-36, column 9, lines 16-23, and column 12, lines 1-8 of the '727 patent. In addition, the WO 00/54762 publication (copy enclosed) discloses that reaction of HA with carbodiimide results in an O-acylisourea derivative that, in the absence of a nucleophile, undergoes an intramolecular rearrangement to the N-acylurea derivative. *See*, page 6, line 30 to page 7, line 6 of this PCT publication. This section further discloses that in the presence of a nucleophile such as a primary amine (*e.g.*, the primary amine on L-lysine methyl ester), the amide derivative of HA is formed. Thus, the art at the time the present application was filed recognized that reacting HA with carbodiimide would result in acylurea bonds rather than ester bonds, and that further reaction with an amine would result in an amide linkage. *See, also*, Xiaobin Zhao's Declaration (enclosed herewith). As such, the processes of Tomihata *et al.* would not have resulted in formation of bonds as recited in claim 1, and thus the Tomihata *et al.* reference does not anticipate the present claims.

In light of the above, Applicant respectfully requests withdrawal of the rejection of claims 1, 2, 4, 12-13, 15, 18, and 20-21 under 35 U.S.C. § 102(b).

Rejection under 35 U.S.C. § 103

The Examiner rejected claims 1-4, 9, 12-21, and 24-35 under 35 U.S.C. § 103(a) as being unpatentable over the Tomihata *et al.* reference in combination with the Nguyen patent (U.S. Patent No. 5,690,961). The Examiner stated that the Tomihata *et al.* reference differs from the presently claimed invention in that Tomihata *et al.* do not teach cross-linking each type of functional group sequentially, does not teach multiple cross-linked HA in the form of a gel, and does not teach a composition further comprising one or more therapeutically active agents. In

addition, the Examiner stated that the Nguyen patent teaches HA cross-linked with dianhydrides via ester bonds, which forms a molecular cage in which molecules with pharmacological activity can be dispersed. The Examiner also stated that the gels, films, threads, particles, or sponges of cross-linked HA can be placed where the contained pharmacological substance is needed. The Examiner alleged that it would have been obvious to a person of ordinary skill at the time of invention to cross-link each type of functional group sequentially, since the selection of any order of performing process steps is *prima facie* obvious in the absence of new or unexpected results. The Examiner also alleged that it would have been obvious to use the multiple cross-linked HA of Tomihata *et al.* as a drug delivery vehicle, since cross-linked HA is well known in the art as a drug delivery vehicle, and since the selection of a known material based on its suitability for its intended use is *prima facie* obvious.

Applicant respectfully disagrees. The teachings of the Tomihata *et al.* reference are not accurate. As discussed above, while the Tomihata *et al.* reference reports that ester bonds result from reacting HA with carbodiimide, subsequent work (*e.g.*, the '727 patent and the WO 00/54762 publication, both submitted herewith) teaches that such reaction will in fact result in acylurea bonds, not ester bonds. *See, also*, Xiaobin Zhao's Declaration (enclosed herewith). Thus, a person having ordinary skill in the art at the time Applicant filed would have been well aware of the inaccuracies of the Tomihata *et al.* reference and that reacting HA with a carbodiimide would result in acylurea bonds rather than ester bonds. In fact, a person having ordinary skill in the art would have appreciated that the Tomihata *et al.* reference suggests, at most, using carbodiimide to crosslink HA and at no point discloses any teaching that provides a skilled artisan with a reasonable expectation of success in achieving HA crosslinked with an ester bond.

The Nguyen patent discloses HA that is cross-linked with polyanhydrides, as well as HA that is cross-linked to polycarboxylic acids. *See, e.g.*, column 3, lines 13-33 of the Nguyen patent. At no point, however, does the Nguyen patent suggest that a person of ordinary skill in the art should make HA cross-linked through two or more different types of bonds as recited in present claim 1. Taken together, the skilled artisan following the teachings of the Tomihata *et al.* reference and the Nguyen patent would not have arrived at HA cross-linked with two or more

bonds selected from the group consisting of ether, ester, sulfone, amine, imino, and amide bonds. This is especially true given that HA cross-linked with carbodiimide was known to result in an acylurea bond, not an ether, ester, sulfone, amine, imino, or amide bond. Thus, the combination of cited references fails to render the present claims obvious.

In light of the above, Applicant respectfully requests withdrawal of the rejection of claims 1, 2, 4, 9, 12-15, 18-21, 24-26, and 29 under 35 U.S.C. § 103(a).

Claim objections

The Examiner objected to claims 5-8 and 11 as being dependent on a rejected base claim. The Examiner stated that these claims would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Applicant acknowledges the Examiner's statement regarding claims 5-8 and 11. In view of the remarks presented herein, Applicant has not amended these claims.

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CONCLUSION

Applicant submits that claims 1, 2, 4-9, 12-15, 18-21, 24-26, 29 and 36 are in condition for allowance, which action is respectfully requested. The Examiner is invited to telephone the undersigned agent if such would further prosecution.

Enclosed is a check for the Petition for Extension of Time fee. Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

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